REMARKS/ARGUMENTS

The Amendments set out above and the following remarks are responsive to the points raised by the Office Action dated March 17, 2009. In view of the amendments set out above and the following remarks, reconsideration is respectfully requested.

The Pending Claims

Claims 1-40, 42-93, 99, and 103 are cancelled, so that claims 41, 94-98, 100-102, and 104-111 are pending. Claim 41 is amended to describe the invention more clearly. The dependencies of claims 100 and 104 are amended to reflect the cancellation of claims 99 and 103, respectively. Claim 94 is amended to provide antecedent basis for language recited in amended claim 41. No new matter is added, and the basis for the amended claim language may be found within the original specification, claims, and drawings. Claim 41 is supported at, for example, original claim 41, Examples 5 and 6, and paragraphs [0018], [0034]-[0035], [0043], [0050], [0051], and [0053] of the specification.

Claim Objection

Claim 41 was objected to on the grounds that it encompasses more than one invention as defined in the Restriction Requirement mailed July 8, 2002. According to the Office Action, the elected invention of Group I is directed to dual specific lymphocytes and an *ex vivo* method of preparing such, and during prosecution of the application, claim 41 has been amended to a form that reads on both *ex vivo* and *in vivo* methods. Claim 41 is amended to recite contacting lymphocytes in a mixed population of T lymphocytes *ex vivo*, thus obviating the objection to the claim.

Rejections under 35 U.S.C. § 112

Claims 41 and 94-111 were rejected under § 112, first paragraph, as failing to comply with the written description requirement.

According to the Office Action, claim 41 recites contacting lymphocytes "in a mixed population of cells," which embraces any mixed population of cells that contains

lymphocytes. The Office Action alleges that the only mixed population of cells disclosed in the specification are tumor infiltrating lymphocytes or T lymphocytes.

The Office Action further alleges that the claims are inclusive of a genus of cells allogeneic to one or more lymphocytes, which embraces any cell type known to exist. According to the Office Action, the only allogeneic cells capable of stimulating lymphocytes are antigen-presenting cells as listed for example, in Figure 13, i.e., dendritic cells, B lymphocytes, and peripheral blood mononuclear cells (PBMCs).

In addition, the Office Action alleges that the claims are inclusive of a genus of endogenous receptors that are reactive with an allogeneic cell, however, the specification fails to teach another "endogenous" receptor beyond a T cell receptor (TCR) that performs the function of and is suitable for use in the claimed invention.

The Office Action further alleges that the claims are inclusive of a genus of "chimeric receptor" that is reactive with a tumor antigen. According to the Office Action, the only type of chimeric receptor disclosed in the specification is a fusion receptor between a single chain antibody that recognizes a tumor antigen and a TCR capable of triggering T cell signal transduction.

This rejection regarding the written description requirement is respectfully traversed. However, in order to expedite matters and allow the application to pass to issuance quickly, claim 41 is amended to recite contacting lymphocytes "in a population of T lymphocytes" and that the allogeneic cell is "selected from the group consisting of dendritic cells, B lymphocytes, and peripheral blood mononuclear cells (PBMCs)." Claim 41 is also amended to change "endogenous receptor" to "T cell receptor." Claim 41 is also amended to change "chimeric receptor" to a "fusion receptor between a single chain antibody that recognizes a tumor antigen and a T cell receptor capable of triggering T cell receptor signal transduction," as suggested by the Office Action. Accordingly, it is respectfully submitted that with these amendments to claim 41, the written description rejection has been overcome.

Claims 41-and 94-111 were rejected under § 112, first paragraph, as lacking enablement.

The Office Action alleges that the claims broadly encompass preparing any type of dual specific lymphocytes and alleges that since the selection and amplification can depend on TCRs, the end product could only be T lymphocytes. According to the Office Action, it was not known and the specification fails to teach any mixed cell population and any allogeneic cell would perform the recited function. The Office Action further alleges that the specification also fails to teach how to isolate the desired lymphocytes from mixed cell types and that the specification fails to provide an enabling disclosure for what is now claimed.

This rejection regarding enablement is respectfully traversed. However, in order to expedite matters and allow the application to pass to issuance quickly, claim 41 is amended to recite that the dual specificity lymphocytes are T lymphocytes (previously recited in claim 99, which has now been cancelled). It is noted that the application describes and fully enables the production of dual specificity T lymphocytes at, e.g., Examples 4 and 7-9. In view of the amendments described above, the remaining grounds for the enablement rejection have been rendered moot. Accordingly, it is respectfully submitted that the enablement rejection has been overcome.

Claims 41 and 94-111 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite on the grounds that the phrase "a mixed population of cells" is unclear. The Office Action alleges that it is unclear what "mixed" embraces or excludes.

This rejection regarding indefiniteness is respectfully traversed. However, in order to expedite matters and allow the application to pass to issuance quickly, claim 41 is amended to recite contacting lymphocytes "in a population of T lymphocytes." Accordingly, it is respectfully submitted that with this amendment to the claim 41, the indefiniteness rejection has been overcome.

Rejection under 35 U.S.C. § 103

Claims 41, 94-103, 105, 106, and 108-111 are rejected under 35 U.S.C. § 103 as allegedly obvious over Hwu et al., *Cancer Res.* 55: 3369-3373 (1995) (hereinafter, "Hwu") in view of Munz et al., *J. Immunol.* 162: 25-34 (1999) (hereinafter, "Munz").

Claim 104 is rejected under § 103 as allegedly unpatentable over Hwu in view of Munz as applied to claims 41, 94-103, 105, 106, and 108-111, and further in view of U.S. Patent No. 5,844,075 to Kawakami et al. (hereinafter, "Kawakami").

Claim 107 is rejected under § 103 as allegedly unpatentable over Hwu in view of Munz as applied to claims 41, 94-103, 105, 106, and 108-111, and further in view of U.S. Patent No. 6,410,319 to Raubitschek et al. (hereinafter, "Raubitschek").

Each of these rejections is separately and respectfully traversed.

The Applicants maintain that the presently claimed method is not obvious to one of ordinary skill in the art over the cited combination of references for the reasons of record and because successfully generating a potent immune response against a tumor antigen using dual specificity T cells is difficult, and at best, unpredictable.

The Applicants submitted with the previous response, filed January 19, 2009, a declaration under 37 CFR §1.132 of Dr. Patrick Hwu ("the Hwu declaration"). In the Hwu declaration, Dr. Hwu explains that successfully generating a potent immune response against a tumor antigen using dual specificity T cells is difficult, and at best, unpredictable (Hwu declaration, ¶ 5). As explained by Dr. Hwu, tumor antigens are generally weak antigens (see, e.g., Kershaw, page 1221, 1st par. and Murphy et al., page 505, 1st full par. left column) (Hwu declaration, ¶ 5). Accordingly, tumor antigens are not potent enough to generate an immune response to a tumor while allogeneic cells are powerful immunogens, but are not capable of generating a specific immune response to a tumor, as Dr. Hwu explains (Hwu declaration, ¶ 5).

The Office Action alleged that the declaration was not persuasive because the instant claims are directed to an *in vitro* method of preparing dual specific T cells, not a method for generating a potent immune response against a tumor antigen *in vivo*.

Amended claim 41 recites that the dual specificity T lymphocytes that are produced by the claimed method generate an anti-tumor immune response *in vivo*. In contrast, Example 1 of the present application shows that cells that are not selected and specifically amplified by contact with an allogeneic cell, as claimed in claim 41, fail to generate an anti-tumor immune response *in vivo*. In Example 1, the T-cells are generated by a method similar

to that described in Hwu using co-cultures with syngeneic cells instead of the claimed allogeneic cells. As explained by Dr. Hwu, despite specific *in vitro* reactivity of MOv-PBL against ovarian cancer cells, none of the eight patients with advanced ovarian cancer responded to infusion of these lymphocytes (Hwu declaration, ¶ 8). As Dr. Hwu further attests, the majority of transduced cells were undetectable in circulation between 12-31 days following MOv-PBL infusion (see also, the patent application, Example 1 and Figure 2) (Hwu declaration, ¶ 8). Accordingly, because the claimed method produces dual specificity T lymphocytes that generate an anti-tumor immune response *in vivo* in contrast to the failure of cells that are not selected and specifically amplified by contact with an allogeneic cell to generate an anti-tumor response *in vivo*, the Hwu declaration must be given weight, and the instant claims are not obvious over the cited references.

Moreover, it must be noted that the method of Example 1 does not read on the instant claims, as alleged by the Office Action. In Example 1, the T-cells are generated by a method similar to that described in Hwu using co-cultures with syngeneic cells instead of the claimed allogeneic cells.

In addition, as Dr. Hwu attests, a T-cell that expresses two distinct receptors can exhibit "cross-antagonism," in which the binding of a ligand to one receptor can inhibit a response to the second receptor (Hwu declaration, ¶ 6). One study, for example, used cell lines that expressed two receptors with different specificities and evaluated whether engagement of one receptor by a peptide would result in inhibition of activation of the T cell line when stimulated by another peptide (Yang et al., *J. Immunol.,* 170: 4532-38 (2003), (hereinafter, "Yang"). Yang showed that an antagonist for one receptor inhibited cell proliferation in response to stimulation of the other receptor (cross-antagonism) in both class I and class II-restricted, dual-specificity T cells (Yang, page 4536, right column, last par.) (Hwu declaration, ¶ 6). Therefore, the Applicants maintain that the success of the dual specificity T cells produced by the claimed method in generating an anti-tumor immune response *in vivo* would not be predictable.

The Office Action alleges that the Hwu declaration is not persuasive because TCR antagonism occurs when one TCR antagonist interferes with another TCR during an immune response. The Office Action alleges that this is highly unlikely in the instant case wherein the structure of the alloreactive TCR and the chimeric tumor-specific receptor are remarkably

different for an antagonist to exist. The Office Action alleges that the step of allogeneic reaction occurs before or separate from transducing with the chimeric receptor and alleges that no interference is likely to happen.

The Office's arguments appear to be incorrectly premised on the assumption that cross-antagonism only occurs when an antagonist binds to two different receptors that are structurally similar to one another. This is not the only mechanism by which cross-antagonism could occur. As explained by Yang, cross-antagonism that inhibits T cell proliferation could involve other mechanisms besides TCR occupancy, such as sequestration of downstream signaling molecules that are present in limiting quantities or the generation of a negative signaling pathway by the antagonist that suppresses the agonist-induced activation pathway (Yang, abstract; p. 4537, paragraph bridging the left and right columns to page 4538). Thus, it does not matter if the structure of the alloreactive TCR and the chimeric tumor-specific receptor are remarkably different or that allogeneic reaction occurs before or separate from transducing with the chimeric receptor. It cannot be ruled out that possible cross-antagonism makes the production of a dual specificity T lymphocyte that generates an anti-tumor immune response *in vivo* unpredictable. Accordingly, the Hwu declaration must be given weight evidencing the patentability of the claimed method which, in an unpredictable field, nevertheless successfully produces a dual specificity T lymphocyte that generates an anti-tumor immune response *in vivo*.

The Office Action also alleges that the declaration is not persuasive because the teaching of Hwu provides that the dual reactive T cells are not concerned with TCR antagonism.

Hwu does not discuss TCR antagonism or provide any teachings whatsoever regarding TCR antagonism. Therefore, it cannot be said that the teaching of Hwu provides that the dual reactive T cells are not concerned with TCR antagonism. Thus, Hwu does not rebut the Applicants' argument that the possibility of cross-antagonism exists and makes the successful production of dual specificity T lymphocytes that generate an anti-tumor immune response *in vivo* unpredictable.

The Hwu declaration also explained that another difficulty in generating a potent immune response against a tumor antigen using dual specificity T cells is that because the

potency of the alloreactive response is so strong, the alloreactive response commandeers the internal "machinery" of the cell (such as, e.g., ZAP 70, and kinases for signal transduction) (Hwu declaration, ¶ 7). Therefore, it would not be expected that the introduction into and expression of an exogenous chimeric receptor in the alloreactive cell to produce "dual specificity lymphocytes" would be successful (Hwu declaration, ¶ 7).

The Office further alleges that this argument is not persuasive because Munz established that for an *ex vivo* activation and expansion process, using an allogeneic cell as a T cell stimulus is comparable to the syngenic/autologous stimulation in obtaining potent tumor reactive CTL cells and produces high avidity CTLs.

The Hwu declaration nevertheless sets forth a difficulty in generating a potent immune response against a tumor antigen, i.e., the commandeering of the internal machinery of the cell, which would make the production of a dual specificity T lymphocyte that generates an anti-tumor immune response *in vivo* unpredictable. Accordingly, the Hwu declaration must be given weight evidencing the patentability of the claimed method which, in an unpredictable field, nevertheless successfully produces a dual specificity T lymphocyte that generates an anti-tumor immune response *in vivo*.

In contrast to the difficulty and unpredictability of generating a potent immune response against a tumor antigen using dual specificity T cells and in contrast to the poor clinical results achieved as described above, T-cells generated in accordance with the claimed method provided superior experimental results in mice.

As explained by Dr. Hwu and as described in Example 5 of the present application, mice received dual specificity T-cells comprising a receptor reactive with the allogeneic cell that were transduced with a receptor which is reactive with a tumor antigen (MOv-γ) (Hwu declaration, ¶ 10). After challenge with ovarian cancer tumor cells, *in vivo* immunization with allogeneic splenocytes from donor mice, combined with administration of dual specificity T cells comprising the receptor reactive with the allogeneic cell that were transduced with a receptor which is reactive with a tumor antigen (MOv-γ), protected mice much more significantly than T cells alone (Figure 5 of the instant patent application). As explained by Dr. Hwu, the combined conditions result in 100% tumor-free mice while mice

infused with dual specificity T cells alone resulted in 25% tumor-free mice (Hwu declaration, ¶ 10). These results were also published in Kershaw (see page 1223, left column, Figure 5A).

As further explained by Dr. Hwu, Example 6 of the present application further illustrates that dual specificity T cells that were produced according to the claimed method provided superior experimental results in mice, in contrast to the poor clinical results described above. In Example 6, mice were injected with tumor cells. Three days later, the mice received either dual specificity T-cells comprising a receptor reactive with the allogeneic cell that were transduced with a receptor which is reactive with a tumor antigen (MOv-γ), non-dual specific T cells, or no treatment. Mice were then immunized with allogeneic splenocytes on days 5, 8, and 11. The dual specificity T cells inhibited the tumor and this effect was augmented by immunization. As explained by Dr. Hwu and as shown in Figure 6 of the patent application, mice that were injected with dual specificity T-cells comprising a receptor reactive with the allogeneic cell that were transduced with a receptor which is reactive with a tumor antigen and immunization or boost, resulted in the smallest tumor size throughout the time course of 29 days (Hwu declaration, ¶ 12). These results were also published in Kershaw (see page 1223, left column, Figure 5B).

Because the presently claimed methods produce dual specificity T-cells that generate an anti-tumor immune response *in vivo* in contrast to the unpredictability and difficulty of generating a potent immune response against a tumor antigen using dual specificity cells, as illustrated by the Hwu declaration, and in contrast to the poor clinical results described above, the presently claimed methods cannot be considered obvious over the cited references to one of ordinary skill in the art.

Because independent claim 41 is allowable for the reasons set forth above, the dependent claims are allowable because they depend from and include the limitations of independent claim 41.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the

prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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Amendment or ROA - Regular (JMJ/SML/mlg)